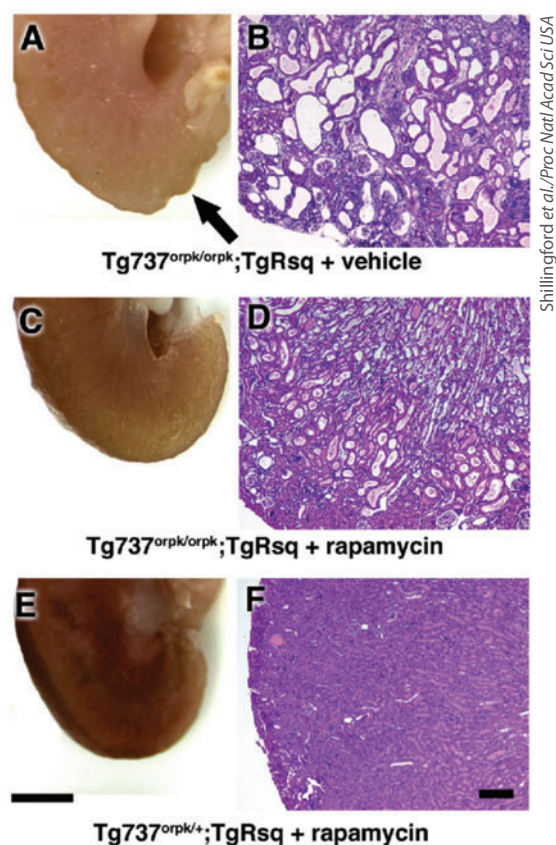


Medical therapy for renal cystic disease

In autosomal-dominant polycystic kidney disease (ADPKD), excessive proliferation of renal epithelial cells leads to cysts that eventually replace most of the normal tissue and cause renal failure. Mutations in the *PKD1* gene, which encodes polycystin-1 (PC1), account for more than 85% of ADPKD cases. PC1 is a multispanning membrane protein with a C-terminal cytoplasmic tail which has been implicated in several signaling pathways. Recent evidence suggests that PC1 may also play a role in cilia-mediated sensing of luminal fluid flow by renal epithelial cells. However, it is unknown which of these proposed functions is critical for renal cyst formation. Mutations in several genes unrelated to PC1 can also lead to a renal cystic phenotype in animal models and humans, but it is unclear whether all of these genotypes may converge on a common pathway that is critical for cyst formation. If such a common pathway exists, it would provide an excellent target for treatment strategies. Shillingford *et al.* examined the possibility that PC1 may act in a common pathway with tuberin, the product of the tuberous sclerosis complex 2 (*TSC2*) gene.¹ *TSC2* mutations lead to tuberous sclerosis, a disease characterized by renal cysts and benign tumors in multiple

organs. Tuberin regulates the kinase activity of mTOR, which has essential roles in protein translation, cell growth, and proliferation. A possible role of mTOR in renal cystic disease is supported by two recent reports indicating that an inhibitor of mTOR slows disease progression in the Han:SPRD rat model.² Indeed, Shillingford *et al.* found that the C-terminal cytoplasmic tail of PC1 interacts with tuberin. The mTOR pathway is inappropriately activated in cyst-lining epithelial cells in human ADPKD and three mouse models with different affected genes, suggesting that this is a common, convergent event during renal cystogenesis. Shillingford *et al.* also found that rapamycin, a clinically used drug and a specific mTOR inhibitor, was highly effective in reducing cystogenesis in two mouse models of polycystic kidney disease and reduced renal size in end-stage ADPKD patients after renal transplantation. These results indicate that dysregulation of mTOR underlies changes in renal epithelial cells that cause the formation of polycystic kidneys in multiple genetic backgrounds. They also provide a mechanistic link among PC1, tuberin, and mTOR, suggesting that rapamycin and related drugs that target the mTOR pathway are excellent candidates for a therapeutic approach to prevent or delay the onset of polycystic kidney disease. (¹*Proc Natl Acad Sci USA* 2006; **103**: 5466–5471. ²*J Am Soc Nephrol* 2005; **16**: 46–51)

Juan Oliver



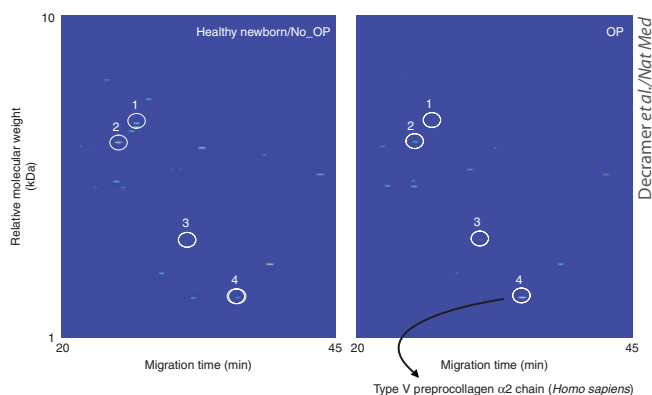
Neuropsychological and renal effects of dental amalgam in children

There is concern that exposure to mercury released by amalgam dental restorations causes adverse health effects, but no randomized trials have examined this premise to date. Two clinical trials recently reported examined the neuropsychological and renal effects of dental amalgam in children. In the new study by Bellinger *et al.*,¹ 534 children aged 6–10 years at baseline were randomly assigned to receive either amalgam ($n = 267$) or resin composite ($n = 267$) materials for dental restoration. The amalgam group had significantly higher mean urinary mercury levels, but no statistically significant differences were found either in the IQ scores and other neurocognitive test results or in urinary albumin after 5 years. In a similarly designed study from Lisbon, Portugal, reported by DeRouen *et al.*,² 507 children aged 8–10 years were followed for 7 years; again, despite higher urinary mercury in the amalgam group, there were no statistically significant differences between the groups' scores on neurobehavioral assessment or nerve conduction velocity tests. In a related editorial, the important information provided by these studies was acknowledged and the studies' limitations discussed,

including the limited follow-up period, the possibility that small effects might have been missed owing to statistical underpowering, and the fact that certain subsets of patients could be more vulnerable than others to the effects of mercury. (¹JAMA 2006; **295**: 1775–1783; ²JAMA 2006; **295**: 1784–1792)

Jai Radhakrishnan

Predictive value of urinary proteome analysis



Proteome analysis is starting to be used for identification of biomarkers for diagnosis of diseases or disease staging. In addition, noninvasive proteomics could be used for prognosis of medical conditions. Congenital unilateral neonatal ureteropelvic junction (UPJ) obstruction can be detected by echography *in utero*, and it is a common clinical problem after birth. The critical issue in infants with UPJ obstruction is determining whether corrective surgery is indicated. Currently, this often requires prolonged medical surveillance, including repetitive invasive diuretic renograms that rely on arbitrary threshold values. In addition, during surveillance, the obstruction might initiate processes that reduce nephron numbers. Urinary markers for UPJ obstruction have been identified, but their prognostic value in terms of informing the decision to operate has not been shown. Using an on-line combination of capillary electrophoresis and mass spectrometry (CE-MS), Decramer *et al.* analyzed urinary polypeptides from individuals with neonatal UPJ obstruction to predict which individuals with this condition would evolve toward obstruction that needed surgical correction. They identified polypeptides that enabled diagnosis of the severity of obstruction and validated these biomarkers in urine collected in a prospective blinded study. Using these biomarkers, they were able to predict, several months in advance and with 94% precision, the clinical evolution of neonates with UPJ obstruction. The combination of classical clinical analysis (determination of pelvic dilation, grade of hydronephrosis, and analysis of renal function and integrity using scintigraphy) and noninvasive CE-MS analysis early

in life to diagnose and predict the clinical evolution of UPJ obstruction should allow early and justified intervention and reduce the number of invasive analyses performed on newborns. (*Nat Med* 2006; **12**: 398–400)

Juan Oliver

Mechanism of insulin resistance

Insulin resistance is a cardinal feature of type 2 diabetes as well as a wide range of other clinical and experimental conditions, such as pregnancy, sepsis, cancer cachexia, obesity, starvation, acromegaly, burn trauma, and metabolic syndrome. It is currently unknown why insulin resistance occurs in so many contexts, but epidemiological studies have shown that it markedly increases cardiovascular disease risk. It also is unknown whether the various insults that trigger insulin resistance act through a common mechanism or use distinct cellular pathways. In an exciting communication, Houstis *et al.* report a genomic analysis of two cellular models of insulin resistance, one induced by treatment with the cytokine tumor necrosis factor- α and the other induced by the glucocorticoid dexamethasone.¹ Gene expression analysis indicated that genes related to generation of reactive oxygen species (ROS) levels were increased in both models, and this was confirmed through measures of cellular redox state. Additional evidence that ROS are involved in insulin resistance was obtained in cell culture experiments using six treatments designed to alter ROS levels, including two small molecules and four transgenes; all ameliorated insulin resistance to varying degrees. One of these treatments was tested in obese, insulin-resistant mice and was shown to improve insulin sensitivity and glucose homeostasis. Together, these findings suggest that increased ROS levels are an important trigger for insulin resistance in numerous settings.

In a related publication, Du *et al.* show that, in the absence of insulin, increased oxidation of free fatty acids (FFAs) in aortic endothelial cells increased production of superoxide by the mitochondrial electron transport chain.² FFA-induced overproduction of superoxide activated a variety of proinflammatory signals previously implicated in hyperglycemia-induced vascular damage and inactivated two important antiatherogenic enzymes, prostacyclin synthase and endothelial nitric oxide synthase (eNOS). In two non-diabetic rodent models — insulin-resistant, obese Zucker (*fa/fa*) rats and high-fat diet-induced insulin-resistant mice — inactivation of prostacyclin synthase and eNOS was prevented by inhibition of FFA release from adipose tissue; by inhibition of the rate-limiting enzyme for fatty acid oxidation in mitochondria, carnitine palmitoyltransferase I; and by reduction of superoxide levels. These studies identify ROS as critical mechanisms for development as well as for the consequences of insulin resistance. (¹*Nature* 2006; **440**: 944–948. ²*J Clin Invest* 2006; **116**: 1071–1080)

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